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### (54) ENTERIC COATED PREPARATION COATED BY SOLVENTLESS ENTERIC COATING AGENT USING LIQUID STATE PLASTICIZER

(57)Abstract:

PURPOSE: To obtain an enteric coated preparation coated with a fine powdery enteric coating agent while sprinkling a liquid state plasticizer to a solid medicine.

CONSTITUTION: This enteric coated preparation is obtained by coating a granular preparation, a powdery preparation or a bulk medicine with a fine powdery enteric coating agent having  $\leq 10\mu\text{m}$  particle diameter (e.g. hydroxypropyl methyl cellulose acetate succinate) while sprinkling a liquid state plasticizer at a room temperature (e.g. triethyl citrate). By the solventless coating not requiring the drying and completed in a short period, the enteric coated preparation having an acid resistance is obtained. Since the drying of solvent is not necessary and the coating time is short, it is possible to shorten the manufacturing process and by the solventless coating, it is possible to apply it to medicines unstable to water and organic solvents. Further, a surfactant, etc., commonly used in an aqueous enteric coating as a dispersing agent, are not necessary.

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**TECHNICAL FIELD**

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[Industrial Application] This invention relates to an enteric coated preparation. It is related with the enteric coated preparation which covered solid drugs with the non-solvent enteric coating agent which uses a liquid plasticizer in more detail.

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PRIOR ART

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[Description of the Prior Art] Or enteric coating protects a weak drug from gastric acid in an acid, it is widely used for the various purpose of protecting gastric mucosa from the drug which has the stimulus to stomach walls, and a trauma.

[0003] If it considers as an enteric coating agent, by the cellulose system, polyvinyl alcohol acetate phthalate (PVAP) is used by the vinyl system, and methacrylic acid and the copolymer of an ethyl acrylate are used for cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), hydroxypropyl-methylcellulose acetate succinate (HPMCAS), and carboxy methyl ethyl cellulose (CMEC) by acrylic.

[0004] These coating agents can dissolve and use a polymer for an organic solvent, or can use it for coating as an aqueous latex or a water dispersion. In order to use an organic solvent or water as a solvent by any approach, the spray of these coating liquid took long duration, and the drying time of a solvent was also required. In order to dislike contact to water or an organic solvent depending on a drug, development of the enteric coating approach which does not use a solvent was desired.

[0005] Since waxes have the property which is not dissolved in water by hydrophobicity, it is used widely by control of the elution of a sustained release drug. Combination with these waxes and enteric coating agents, for example, in Provisional Publication No. No. 164114 [ 56 to ] The approach of carrying out enteric coating to the granulation which carried out wet agglomeration by the presentation containing a higher fatty acid or its metal salt by the well-known approach conventionally in Provisional Publication No. No. 33128 [ 62 to ] As an enteric coated preparation of interferon, a micell is prepared by the drainage system from unsaturated fatty acid and a surfactant. After freeze-drying this thing and fabricating into granulation etc., performing enteric coating in Provisional Publication No. No. 20219 [ 59 to ] Coating with the presentation which contains a higher fatty acid in undershirt coating of an enteric coated preparation in Provisional Publication No. No. 46019 [ 58 to ] Dissolving an enteric coating agent and fats and oils in common solvents (ethanol, dichloroethane, etc.) at coating of the gradual release section of the sustained release drug of nifedipine, and using for coating is proposed.

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TECHNICAL PROBLEM

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[Problem(s) to be Solved by the Invention]

[0006] However, although each of these coating approaches is using waxes and enteric coating together, conventionally, the enteric coating itself is the well-known approach for which the solvent was used, and coating and desiccation take it long duration.

[0007] As an approach of coating waxes In the publication number No. 287019 [ one to ], for example, as lipid nature matter with a melting point of 40 degrees C or more Heat a higher fatty acid, higher alcohol, and higher-fatty-acid ester more than the melting point, or it dissolves in an organic solvent. A coating pan or centrifugal flow mold coating granulator is used. The method of performing ethyl cellulose or enteric coating, after covering with a spray in the publication number No. 287021 [ one to ] Although the approach the approach of heating powder or waxes with a melting point [ of a pellet type ] of 40-90 degrees C more than the melting point of a wax, and covering it using fluid bed coating equipment coats a lipid powdery part with a melting point of 40 degrees C or more with the publication number No. 142735 [ two to ] by mechanical stirring is proposed These are a sustained release drug or the pharmaceutical preparation aiming at masking of bitterness, and combination with an enteric coating agent is not touched on to them.

[0008] Moreover, although it is indicated in the publication number No. 292229 [ two to ] that durability pharmaceutical preparation is obtained by heating the mixture of a solid higher fatty acid, an enteric coating agent, and a surfactant in a poorly soluble drug and ordinary temperature, kneading under melting of a higher fatty acid, and \*(ing) a granule, it is not related with an enteric coated preparation with acid resistance. Also in Provisional Publication No. No. 181214 [ 62 to ] as low melting point matter with a melting point of 30-100 degrees C Fats and oils fatty acids and higher alcohol raise -- having -- these complications -- by carrying out adhesion granulation of the drug by melting around it by using the granular low melting point matter as a nucleus, heating the particle further obtained under stirring rolling, and sprinkling and covering talc etc. The method of \*(ing) a sustained-release granular object is indicated, covering with talc is faced by this approach, and it is 10 micrometers. By using together the enteric coating agent pulverized below, although eburation is carried out, it is not related with the enteric coated preparation with acid resistance which is a coat.

[0009] As a result of inquiring wholeheartedly in view of the above-mentioned point, this invention persons find out that the enteric coated preparation which has acid resistance by non-solvent coating which is covering with an enteric impalpable powder-like coating agent, sprinkling a liquid-like plasticizer, and does not need desiccation for a short time is obtained, and came to complete this invention.

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MEANS

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[Means for Solving the Problem] That is, this invention offers the enteric coated preparation which covered the enteric impalpable powder-like coating agent, sprinkling a liquid-like plasticizer to solid drugs.

[0011] Moreover, this invention offers the enteric coated preparation said whose solid drugs are a granule, a fine grain agent, or a drug original object.

[0012] Furthermore, this invention offers the enteric coated preparation whose plasticizer of the shape of said liquid is citric-acid triethyl.

[0013] Moreover, this invention offers the enteric coated preparation whose particle diameter of the enteric coating agent of the shape of said impalpable powder is 10 micrometers or less.

[0014] Hereafter, this invention is explained in full detail. The enteric coated preparation by this invention is characterized by covering with an impalpable powder-like enteric coating basis, sprinkling a liquid-like plasticizer in ordinary temperature to solid drugs.

[0015] It will not be limited especially if it has the property to which welding of the enteric impalpable powder-like coating agent is carried out by hydrophobicity as a plasticizer used for this invention. For example, citric-acid triethyl, a triacetin, dibutyl phthalate, etc. are mentioned. In these, the large citric-acid triethyl of the effectiveness to which welding of the enteric coating agent is carried out is desirable. These plasticizers can be used as one sort or two sorts or more of mixture.

[0016] Moreover, on the occasion of covering of an enteric coating agent, the water resisting property of the enteric coated preparation obtained can be raised by adding hydrophobic waxes, such as higher alcohol, higher fatty acids, and glycerine fatty acid esters.

[0017] Furthermore, it can also consider as a sustained release drug by using together water-soluble polyhydric alcohol, such as a polyethylene glycol.

[0018] In order that this invention may sprinkle and cover the enteric coating agent on impalpable powder, applicable desirable solid drugs are a granule, a fine grain agent, or a drug original object, and since there may be few amounts of the enteric coating agent needed for the thing near a globular form acquiring acid resistance, these are desirable [ drugs ].

[0019] The enteric coating agent used for this invention is 10 micrometers preferably. That what is necessary is just the following impalpable powder By the cellulose system, for example, cellulose acetate phthalate (CAP), Cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), Hydroxypropyl-methylcellulose acetate succinate (HPMCAS), By the vinyl system, polyvinyl alcohol acetate phthalate (PVAP) can use [ carboxy methyl ethyl cellulose (CMEC) ] methacrylic acid and the copolymer of an ethyl acrylate at acrylic. If a mean diameter exceeds 10 micrometers, a coating agent does not adhere to granulation well and may be unable to coat it.

[0020] Among these coating agents, the hydroxypropyl-methylcellulose acetate succinate (HPMCAS) softening temperature excels [ succinate ] in film formation nature low is suitable.

[0021] Moreover, it can also consider as a sustained release drug by using together the impalpable powder of giant molecules other than an enteric coating agent, for example, ethyl cellulose, and an acrylic polymer.

[0022] In order to carry out this invention, and not to use a solvent, great desiccation capacity is not needed, but it is desirable to have spreading of the enteric coating agent of the shape of sprinkled impalpable powder, a certain amount of heating for welding, and stirring capacity, for example, centrifugal flow coating equipment, pan coating equipment, fluid bed coating equipment, etc. are mentioned. In these coating equipments, the centrifugal flow coating equipment which has moderate stirring capacity is suitable.

[0023] while carrying out stirring rolling of the covering by the enteric coating agent with centrifugal flow coating equipment which mentioned above granulation or fine grain-like solid drugs -- ordinary temperature -- a liquid or the liquid-like plasticizer which carried out heating fusion -- spraying -- or a spray is carried out, an enteric coating agent 10 micrometers or less is sprinkled to coincidence, and solid drugs are covered. These actuation of a series of can also be carried out by changing a presentation in several steps, respectively. Moreover, spraying of talc, Aerosil (SiO<sub>2</sub>), magnesium stearate, corn starch, etc. may be used together in order to prevent adhesion of the granulation at the time of covering.

[0024] Although the weight ratio of the plasticizer in this invention and an enteric coating agent and the amount of coatings to solid drugs are factors important when acquiring acid resistance Although it changes with the water solubility of the drug to apply, the presentation ratios of the drug in solid drugs (granule etc.), etc. a lot If it is in the range of plasticizer:enteric coating agent = 2:8-8:2 and the presentation ratio of a plasticizer increases more than this in general, the collapsibility in the 2nd liquid (pH6.8) of a Japanese pharmacopoeia will be lost, and, less than [ this ], the welding of an enteric coating agent will become inadequate.

[0025] The amount of coatings is the weight ratio of the covered enteric coating agent to solid drugs, and is in 10 - 50% of the weight of the range in general.

[0026] In addition, in order to sprinkle and coat an enteric coating agent with this invention, even if the amount of coatings increases, the processing time is remarkably short.

[0027] The enteric coated preparation of this invention obtained as mentioned above may be covered with the high molecular compound of next further others. Moreover, the drug and additive {the plasticizer, the coloring agent, the pigment, the antitack agent (talc), and the fats and oils} which are accepted in these coatings usually in galenical pharmacy may be added.

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EXAMPLE

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[Example] Next, although an example explains this invention still more concretely, this invention is not limited to these examples. In addition, number of copies in an example and % are weight %s.

[0029] [Production of experiment 1: VB2 content granulation] Having taught 2000g (non PARERU 101 20-24# Freund Industrial make) of nucleus granulation to centrifugal flow coating equipment (CF coater CF-360 Freund Industrial make), and spraying a hydroxypropylcellulose 5% water solution, the fine particles which mixed VB275g and corn-starch 1175g to homogeneity were sprinkled, and granulation was produced. The content of VB2 in this granulation was 2%.

[0030] [Example 1] 400g of VB22% content granulation produced in the experiment 1 is taught to centrifugal flow coating equipment (CFcoater CF-360 Freund Industrial make), and they are the intake-air temperature of 60 degrees C, 40 degrees C of temperature of goods, and rotational frequency 200rpm, Carrying out the spray of the citric-acid triethyl 60g at the rate of 10 g/min, the fine particles which mixed hydroxypropyl-methylcellulose acetate succinate (mean-particle-diameter 5 micrometer: AS-MF Shin-Etsu Chemical Co., Ltd. make) 120g and talc 240g to homogeneity were added at the rate of 60 g/min, and coating was performed. Yield was 95%. The processing time was 6min. The acid resistance which that rate of elution of is 1.5%, and was excellent in this coating granulation as a result of measuring the rate of elution 2 hours after the 1st liquid according to Japanese pharmacopoeia 12 dissolution test was shown. Moreover, according to Japanese pharmacopoeia 12 disintegration test, when the decay time in the 2nd liquid of the granulation is measured, it is 10min, and it turned out that enteric is shown.

[0031] [Example 2] 400g of VB22% content granulation produced in the experiment 1 is taught to centrifugal flow coating equipment (CFcoater CF-360 Freund Industrial make), and they are the intake-air temperature of 60 degrees C, 40 degrees C of temperature of goods, and rotational frequency 200rpm, Carrying out the spray of the triacetin 120g at the rate of 20 g/min, the fine particles which mixed hydroxypropyl-methylcellulose acetate succinate (mean-particle-diameter 5 micrometer: AS-MF Shin-Etsu Chemical Co., Ltd. make) 120g and talc 240g to homogeneity were added at the rate of 60 g/min, and coating was performed. Yield was 95%. The processing time was 6min. The acid resistance which that rate of elution of is 1.5%, and was excellent in this coating granulation as a result of measuring the rate of elution 2 hours after the 1st liquid according to Japanese pharmacopoeia 12 dissolution test was shown. Moreover, according to Japanese pharmacopoeia 12 disintegration test, when the decay time in the 2nd liquid of the granulation is measured, it is 10min, and it turned out that enteric is shown.

[0032] [Example 3] 400g of VB22% content granulation produced in the experiment 1 is taught to centrifugal flow coating equipment (CFcoater CF-360 Freund Industrial make), and they are the intake-air temperature of 60 degrees C, 40 degrees C of temperature of goods, and rotational frequency 200rpm, Carrying out the spray of the 120g of the ethanol 50% solutions of citric-acid triethyl at the rate of 20 g/min, the fine particles which mixed hydroxypropyl-methylcellulose acetate succinate (mean-particle-diameter 5 micrometer: AS-MF Shin-Etsu Chemical Co., Ltd. make) 120g and talc 120g to homogeneity were added at the rate of 40 g/min, and coating was performed. Yield was 98%. The processing time was 6min. The acid resistance which that rate of elution of is 1.0%, and was excellent in this coating granulation as a result of measuring the rate of elution 2 hours after the 1st liquid according to Japanese pharmacopoeia 12 dissolution test was shown. Moreover, according to Japanese pharmacopoeia 12 disintegration test, when the decay time in the 2nd liquid of the granulation is measured, it is 11min, and it turned out that enteric is shown.

[0033] [Example 1 of a comparison] The coating liquid of the following presentation was used for hydroxypropyl-methylcellulose acetate succinate (AS-MF Shin-Etsu Chemical Co., Ltd. make) to VB2 granulation produced in the experiment 1, and moisture powder system coating was carried out. 400g of VB2 granulation -- fluid bed coating equipment (Multiplex MP-01 Powrex make) -- teaching -- the intake-air temperature of 80 degrees C, the exhaust-gas temperature of 35 degrees C, and coating liquid spray rate 25 g/min -- the base of hydroxypropyl-methylcellulose acetate succinate (AS-MF Shin-Etsu Chemical Co., Ltd. make) -- coating was carried out until the amount (30%) of coatings to granulation became the same as that of an example 1. Coating yield is 92% and carried out the coating time amount 68min important point. Then, 60 degrees C and 30min desiccation were carried out as post-desiccation. The sum total time amount which coating granulation production took was 98min.

[Coating liquid presentation] hydroxypropyl-methylcellulose acetate succinate (AS-MF) The Shin-Etsu Chemical Co., Ltd. make 7.00 % citric-acid triethyl 1.96 Talc 2.10 Sodium lauryl sulfate 0.21 Water 88.73 A total of 100.00

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EFFECT OF THE INVENTION

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[Effect of the Invention] The conventional enteric coating is performed by the organic solvent solution, aqueous latex, or water dispersion of an enteric coating agent. For this reason, it had troubles, such as a spray taking long duration, and the drying time of a solvent being also required, and disliking contact to water or an organic solvent depending on a drug, or disliking heating at the time of desiccation.

[0035] According to this invention, the enteric coated preparation which has acid resistance by non-solvent coating which does not need desiccation for a short time is obtained. Therefore, by needlessness (with no heating at the time of desiccation), since coating time amount is short, desiccation of a solvent can attain shortening of a production process. Moreover, it is applicable to an unstable drug to water and an organic solvent with non-solvent coating. Furthermore, it has the advantage that it is not necessary to use the surfactant currently used widely as a dispersant by drainage system enteric coating.

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DETAILED DESCRIPTION

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## [Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to an enteric coated preparation. It is related with the enteric coated preparation which covered solid drugs with the non-solvent enteric coating agent which uses a liquid plasticizer in more detail. [0002]

[Description of the Prior Art] Or enteric coating protects a weak drug from gastric acid in an acid, it is widely used for the various purpose of protecting gastric mucosa from the drug which has the stimulus to stomach walls, and a trauma.

[0003] If it considers as an enteric coating agent, by the cellulose system, polyvinyl alcohol acetate phthalate (PVAP) is used by the vinyl system, and methacrylic acid and the copolymer of an ethyl acrylate are used for cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), hydroxypropyl-methylcellulose acetate succinate (HPMCAS), and carboxy methyl ethyl cellulose (CMEC) by acrylic.

[0004] These coating agents can dissolve and use a polymer for an organic solvent, or can use it for coating as an aqueous latex or a water dispersion. In order to use an organic solvent or water as a solvent by any approach, the spray of these coating liquid took long duration, and the drying time of a solvent was also required. In order to dislike contact to water or an organic solvent depending on a drug, development of the enteric coating approach which does not use a solvent was desired.

[0005] Since waxes have the property which is not dissolved in water by hydrophobicity, it is used widely by control of the elution of a sustained release drug. Combination with these waxes and enteric coating agents, for example, in Provisional Publication No. No. 164114 [ 56 to ] The approach of carrying out enteric coating to the granulation which carried out wet agglomeration by the presentation containing a higher fatty acid or its metal salt by the well-known approach conventionally in Provisional Publication No. No. 33128 [ 62 to ] As an enteric coated preparation of interferon, a micell is prepared by the drainage system from unsaturated fatty acid and a surfactant. After freeze-drying this thing and fabricating into granulation etc., performing enteric coating in Provisional Publication No. No. 20219 [ 59 to ] Coating with the presentation which contains a higher fatty acid in undershirt coating of an enteric coated preparation in Provisional Publication No. No. 46019 [ 58 to ] Dissolving an enteric coating agent and fats and oils in common solvents (ethanol, dichloroethane, etc.) at coating of the gradual release section of the sustained release drug of nifedipine, and using for coating is proposed.

## [Problem(s) to be Solved by the Invention]

[0006] However, although each of these coating approaches is using waxes and enteric coating together, conventionally, the enteric coating itself is the well-known approach for which the solvent was used, and coating and desiccation take it long duration.

[0007] As an approach of coating waxes In the publication number No. 287019 [ one to ], for example, as lipid nature matter with a melting point of 40 degrees C or more Heat a higher fatty acid, higher alcohol, and higher-fatty-acid ester more than the melting point, or it dissolves in an organic solvent. A coating pan or centrifugal flow mold coating granulator is used. The method of performing ethyl cellulose or enteric coating, after covering with a spray in the publication number No. 287021 [ one to ] Although the approach the approach of heating powder or waxes with a melting point [ of a pellet type ] of 40-90 degrees C more than the melting point of a wax, and covering it using fluid bed coating equipment coats a lipid powdery part with a melting point of 40 degrees C or more with the publication number No. 142735 [ two to ] by mechanical stirring is proposed These are a sustained release drug or the pharmaceutical preparation aiming at masking of bitterness, and combination with an enteric coating agent is not touched on to them.

[0008] Moreover, although it is indicated in the publication number No. 292229 [ two to ] that durability pharmaceutical preparation is obtained by heating the mixture of a solid higher fatty acid, an enteric coating agent, and a surfactant in a poorly soluble drug and ordinary temperature, kneading under melting of a higher fatty acid, and \*(ing) a granule, it is not related with an enteric coated preparation with acid resistance. Also in Provisional Publication No. No. 181214 [ 62 to ] as low melting point matter with a melting point of 30-100 degrees C Fats and oils fatty acids and higher alcohol raise -- having -- these complications -- by carrying out adhesion granulation of the drug by melting around it by using the granular low melting point matter as a nucleus, heating the particle further obtained under stirring rolling, and sprinkling and covering talc etc. The method of \*(ing) a sustained-release granular object is indicated, covering with talc is faced by this approach, and it is 10 micrometers. By using together the enteric coating agent pulverized below, although eburnation is carried out, it is not related with the enteric coated preparation with acid resistance which is a coat.

[0009] As a result of inquiring wholeheartedly in view of the above-mentioned point, this invention persons find out that the enteric coated preparation which has acid resistance by non-solvent coating which is covering with an enteric impalpable powder-like coating agent, sprinkling a liquid-like plasticizer, and does not need desiccation for a short time is obtained, and came to complete this invention.

[0010]

[Means for Solving the Problem] That is, this invention offers the enteric coated preparation which covered the enteric impalpable powder-like coating agent, sprinkling a liquid-like plasticizer to solid drugs.

[0011] Moreover, this invention offers the enteric coated preparation said whose solid drugs are a granule, a fine grain agent, or a drug original object.

[0012] Furthermore, this invention offers the enteric coated preparation whose plasticizer of the shape of said liquid is citric-acid triethyl.

[0013] Moreover, this invention offers the enteric coated preparation whose particle diameter of the enteric coating agent of the shape of said impalpable powder is 10 micrometers or less.

[0014] Hereafter, this invention is explained in full detail. The enteric coated preparation by this invention is characterized by covering with an impalpable powder-like enteric coating basis, sprinkling a liquid-like plasticizer in ordinary temperature to solid drugs.

[0015] It will not be limited especially if it has the property to which welding of the enteric impalpable powder-like coating agent is carried out by hydrophobicity as a plasticizer used for this invention. For example, citric-acid triethyl, a triacetin, dibutyl phthalate, etc. are mentioned. In these, the large citric-acid triethyl of the effectiveness to which welding of the enteric coating agent is carried out is desirable. These plasticizers can be used as one sort or two sorts or more of mixture.

[0016] Moreover, on the occasion of covering of an enteric coating agent, the water resisting property of the enteric coated preparation obtained can be raised by adding hydrophobic waxes, such as higher alcohol, higher fatty acids, and glycerine fatty acid esters.

[0017] Furthermore, it can also consider as a sustained release drug by using together water-soluble polyhydric alcohol, such as a polyethylene glycol.

[0018] In order that this invention may sprinkle and cover the enteric coating agent on impalpable powder, applicable desirable solid drugs are a granule, a fine grain agent, or a drug original object, and since there may be few amounts of the enteric coating agent needed for the thing near a globular form acquiring acid resistance, these are desirable [ drugs ].

[0019] The enteric coating agent used for this invention is 10 micrometers preferably. That what is necessary is just the following impalpable powder By the cellulose system, for example, cellulose acetate phthalate (CAP), Cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), Hydroxypropyl-methylcellulose acetate succinate (HPMCAS), By the vinyl system, polyvinyl alcohol acetate phthalate (PVAP) can use [ carboxy methyl ethyl cellulose (CMEC) ] methacrylic acid and the copolymer of an ethyl acrylate at acrylic. If a mean diameter exceeds 10 micrometers, a coating agent does not adhere to granulation well and may be unable to coat it.

[0020] Among these coating agents, the hydroxypropyl-methylcellulose acetate succinate (HPMCAS) softening temperature excels [ succinate ] in film formation nature low is suitable.

[0021] Moreover, it can also consider as a sustained release drug by using together the impalpable powder of giant molecules other than an enteric coating agent, for example, ethyl cellulose, and an acrylic polymer.

[0022] In order to carry out this invention, and not to use a solvent, great desiccation capacity is not needed, but it is desirable to have spreading of the enteric coating agent of the shape of sprinkled impalpable powder, a certain amount of heating for welding, and stirring capacity, for example, centrifugal flow coating equipment, pan coating equipment, fluid bed coating equipment, etc. are mentioned. In these coating equipments, the centrifugal flow coating equipment which has moderate stirring capacity is suitable.

[0023] while carrying out stirring rolling of the covering by the enteric coating agent with centrifugal flow coating equipment which mentioned above granulation or fine grain-like solid drugs -- ordinary temperature -- a liquid or the liquid-like plasticizer which carried out heating fusion -- spraying -- or a spray is carried out, an enteric coating agent 10 micrometers or less is sprinkled to coincidence, and solid drugs are covered. These actuation of a series of can also be carried out by changing a presentation in several steps, respectively. Moreover, spraying of talc, Aerosil (SiO<sub>2</sub>), magnesium stearate, corn starch, etc. may be used together in order to prevent adhesion of the granulation at the time of covering.

[0024] Although the weight ratio of the plasticizer in this invention and an enteric coating agent and the amount of coatings to solid drugs are factors important when acquiring acid resistance Although it changes with the water solubility of the drug to apply, the presentation ratios of the drug in solid drugs (granule etc.), etc. a lot If it is in the range of plasticizer:enteric coating agent =2:8-8:2 and the presentation ratio of a plasticizer increases more than this in general, the collapsibility in the 2nd liquid (pH6.8) of a Japanese pharmacopoeia will be lost, and, less than [ this ], the welding of an enteric coating agent will become inadequate.

[0025] The amount of coatings is the weight ratio of the covered enteric coating agent to solid drugs, and is in 10 - 50% of the weight of the range in general.

[0026] In addition, in order to sprinkle and coat an enteric coating agent with this invention, even if the amount of coatings increases, the processing time is remarkably short.

[0027] The enteric coated preparation of this invention obtained as mentioned above may be covered with the high molecular compound of next further others. Moreover, the drug and additive {the plasticizer, the coloring agent, the pigment, the antitack agent (talc), and the fats and oils} which are accepted in these coatings usually in galenical pharmacy may be added.

[0028]

[Example] Next, although an example explains this invention still more concretely, this invention is not limited to these examples. In addition, number of copies in an example and % are weight %s.

[0029] [Production of experiment 1:VB2 content granulation] Having taught 2000g (non PARERU 101 20-24# Freund Industrial make) of nucleus granulation to centrifugal flow coating equipment (CF coater CF-360 Freund Industrial make), and spraying a hydroxypropylcellulose 5% water solution, the fine particles which mixed VB275g and corn-starch 1175g to homogeneity were sprinkled, and granulation was produced. The content of VB2 in this granulation was 2%.

[0030] [Example 1] 400g of VB22% content granulation produced in the experiment 1 is taught to centrifugal flow coating equipment (CFcoater CF-360 Freund Industrial make), and they are the intake-air temperature of 60 degrees C, 40 degrees C of temperature of goods, and rotational frequency 200rpm, Carrying out the spray of the citric-acid triethyl 60g at the rate of 10 g/min, the fine particles which mixed hydroxypropyl-methylcellulose acetate succinate (mean-particle-diameter 5 micrometer:AS-MF Shin-Etsu Chemical Co., Ltd. make) 120g and talc 240g to homogeneity were added at the rate of 60 g/min, and coating was performed. Yield was 95%. The processing time was 6min. The acid resistance which that rate of elution of is 1.5%, and was excellent in this coating granulation as a result of measuring the rate of elution 2 hours after the 1st liquid according to Japanese pharmacopoeia 12 dissolution test was shown. Moreover, according to Japanese pharmacopoeia 12 disintegration test, when the decay time in the 2nd liquid of the granulation is measured, it is 10min, and it turned out that enteric is shown.

[0031] [Example 2] 400g of VB22% content granulation produced in the experiment 1 is taught to centrifugal flow coating equipment (CFcoater CF-360 Freund Industrial make), and they are the intake-air temperature of 60 degrees C, 40 degrees C of temperature of goods, and rotational frequency 200rpm, Carrying out the spray of the triacetin 120g at the rate of 20 g/min, the fine particles which mixed hydroxypropyl-methylcellulose acetate succinate (mean-particle-diameter 5 micrometer:AS-MF Shin-Etsu Chemical Co., Ltd. make) 120g and talc 240g to homogeneity were added at the rate of 60 g/min, and coating was performed. Yield was 95%. The processing time was 6min. The acid resistance which that rate of elution of is 1.5%, and was excellent in this coating granulation as a result of measuring the rate of elution 2 hours after the 1st liquid according to Japanese pharmacopoeia 12 dissolution test was shown. Moreover, according to Japanese pharmacopoeia 12 disintegration test, when the decay time in the 2nd liquid of the granulation is measured, it is 10min, and it turned out that enteric is shown.

[0032] [Example 3] 400g of VB22% content granulation produced in the experiment 1 is taught to centrifugal flow coating equipment (CFcoater CF-360 Freund Industrial make), and they are the intake-air temperature of 60 degrees C, 40 degrees C of temperature of goods, and rotational frequency 200rpm, Carrying out the spray of the 120g of the ethanol 50% solutions of citric-acid triethyl at the rate of 20 g/min, the fine particles which mixed hydroxypropyl-methylcellulose acetate succinate (mean-particle-diameter 5 micrometer:AS-MF Shin-Etsu Chemical Co., Ltd. make) 120g and talc 120g to homogeneity were added at the rate of 40 g/min, and coating was performed. Yield was 98%. The processing time was 6min. The acid resistance which that rate of elution of is 1.0%, and was excellent in this coating granulation as a result of measuring the rate of elution 2 hours after the 1st liquid according to Japanese pharmacopoeia 12 dissolution test was shown. Moreover, according to Japanese pharmacopoeia 12 disintegration test, when the decay time in the 2nd liquid of the granulation is measured, it is 11min, and it turned out that enteric is shown.

[0033] [Example 1 of a comparison] The coating liquid of the following presentation was used for hydroxypropyl-methylcellulose acetate succinate (AS-MF Shin-Etsu Chemical Co., Ltd. make) to VB2 granulation produced in the experiment 1, and moisture powder system coating was carried out. 400g of VB2 granulation -- fluid bed coating equipment (Multiplex MP-01 Powrex make) -- teaching -- the intake-air temperature of 80 degrees C, the exhaust-gas temperature of 35 degrees C, and coating liquid spray rate 25 g/min -- the base of hydroxypropyl-methylcellulose acetate succinate (AS-MF Shin-Etsu Chemical Co., Ltd. make) -- coating was carried out until the amount (30%) of coatings to granulation became the same as that of an example 1. Coating yield is 92% and carried out the coating time amount 68min important point. Then, 60 degrees C and 30min desiccation were carried out as post-desiccation. The sum total time amount which coating granulation production took was 98min.

[Coating liquid presentation] hydroxypropyl-methylcellulose acetate succinate (AS-MF) The Shin-Etsu Chemical Co., Ltd. make 7.00 % citric-acid triethyl 1.96 Talc 2.10 Sodium lauryl sulfate 0.21 Water 88.73 A total of 100.00 [0034]

[Effect of the Invention] The conventional enteric coating is performed by the organic solvent solution, aqueous latex, or water dispersion of an enteric coating agent. For this reason, it had troubles, such as a spray taking long duration, and the drying time of a solvent being also required, and disliking contact to water or an organic solvent depending on a drug, or disliking heating at the time of desiccation.

[0035] According to this invention, the enteric coated preparation which has acid resistance by non-solvent coating which does not need desiccation for a short time is obtained. Therefore, by needlessness (with no heating at the time of desiccation), since coating time amount is short, desiccation of a solvent can attain shortening of a production process. Moreover, it is applicable to an unstable drug to water and an organic solvent with non-solvent coating. Furthermore, it has the advantage that it is not necessary to use the surfactant currently used widely as a dispersant by drainage system enteric coating.

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[Translation done.]

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CLAIMS

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[Claim(s)]

[Claim 1] The enteric coated preparation which covered the enteric impalpable powder-like coating agent, sprinkling a liquid-like plasticizer to solid drugs.

[Claim 2] The enteric coated preparation according to claim 1 said whose solid drugs are a granule, a fine grain agent, or a drug original object.

[Claim 3] The enteric coated preparation according to claim 1 whose plasticizer of the shape of said liquid is citric-acid triethyl.

[Claim 4] The enteric coated preparation according to claim 1 whose particle diameter of the enteric coating agent of the shape of said impalpable powder is 10 micrometers or less.

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(54) 【発明の名称】 液体状可塑剤を用いる無溶媒腸溶性コーティング剤で被覆した腸溶性製剤

## (57) 【要約】

【構成】 固形薬剤に、液体状の可塑剤を散布しつつ微粉末状の腸溶性コーティング剤を被覆した腸溶性製剤である。

【効果】 短時間で乾燥を必要としない無溶媒コーティングにより耐酸性を有する腸溶性製剤が得られる。したがって、溶媒の乾燥が不要でコーティング時間が短いため製造工程の短縮化を図ることができる。また、無溶媒コーティングにより水および有機溶剤に対して不安定な薬物に適用できる。さらに、水系腸溶性コーティングで分散剤として汎用されている界面活性剤なども使用する必要がないという利点を有する。

## 【特許請求の範囲】

【請求項1】 固形薬剤に、液体状の可塑剤を散布しつつ微粉末状の腸溶性コーティング剤を被覆した腸溶性製剤。

【請求項2】 前記固形薬剤が、顆粒剤、細粒剤または薬物原体である請求項1記載の腸溶性製剤。

【請求項3】 前記液体状の可塑剤が、クエン酸トリエチルである請求項1記載の腸溶性製剤。

【請求項4】 前記微粉末状の腸溶性コーティング剤の粒子径が、10 $\mu$ m以下である請求項1記載の腸溶性製剤。

## 【発明の詳細な説明】

## 【0001】

【産業上の利用分野】本発明は、腸溶性製剤に関する。さらに詳しくは、固形薬剤を液体状可塑剤を用いる無溶媒腸溶性コーティング剤で被覆した腸溶性製剤に関する

## 【0002】

【従来の技術】腸溶性コーティングは、酸に弱い薬物を胃酸から保護するあるいは、胃壁に対する刺激、傷害を有する薬物から胃粘膜を保護する等の様々な目的で広く利用されている。

【0003】腸溶性コーティング剤としては、セルロース系では、セルロースアセテートフタレート(CAP)、セルロースアセテートトリメリテート(CAT)、ヒドロキシプロピルメチルセルロースフタレート(HPMCP)、ヒドロキシプロピルメチルセルロースアセテートサクシネート(HPMCAS)、カルボキシメチルエチルセルロース(CMEC)が、ビニル系では、ポリビニルアルコールアセテートフタレート(PVAP)が、アクリル系では、メタアクリル酸とアクリル酸エチルの共重合体が使われている。

【0004】これらのコーティング剤は、ポリマーを有機溶剤に溶解して用いるかまたは水性ラテックスあるいは水分散液として、コーティングに用いることができる。何れの方法によっても、有機溶剤または水を溶媒として用いるため、これらのコーティング液のスプレーに長時間を要し、また、溶媒の乾燥時間も必要であった。薬物によっては、水あるいは有機溶剤との接触を嫌うため、溶剤を使用しない腸溶性コーティング方法の開発が望まれていた。

【0005】ワックス類は、疎水性で水に溶解しない特性を有することから、徐放性製剤の溶出のコントロールに汎用されている。これらのワックス類と腸溶性コーティング剤との組み合わせは、例えば、特開昭第56-164114号では、高級脂肪酸またはその金属塩を含む組成で湿式造粒した顆粒に従来公知の方法で腸溶コーティングする方法が、特開昭第62-33128号では、インターフェロンの腸溶性製剤として、不飽和脂肪酸と界面活性剤から水系でミセルを調製し、このものを凍結乾燥し、顆粒等に成形した後、腸溶コーティングを施す

ことが、特開昭第59-20219号では、腸溶性製剤のアンダーコーティングに高級脂肪酸を含む組成でコーティングすることが、特開昭第58-46019号では、ニフェジピンの徐放性製剤の徐放部のコーティングに腸溶性コーティング剤と油脂類を共通の溶剤(エタノール、ジクロロエタン等)に溶解してコーティングに用いることが提案されている。

## 【発明が解決しようとする課題】

【0006】しかしながら、これらのコーティング方法は何れもワックス類と腸溶コーティングを併用しているが、腸溶コーティング自体は溶剤を用いた従来公知の方法であり、コーティングと乾燥に長時間を要する。

【0007】ワックス類をコーティングする方法としては、例えば、特開平第1-287019号では、融点40℃以上の脂質性物質として、高級脂肪酸、高級アルコール、高級脂肪酸エステル類などを融点以上加熱するか有機溶剤に溶解して、コーティングパンあるいは遠心流動型コーティング造粒装置を用いて、スプレーにより被覆した後エチルセルロースあるいは腸溶性コーティングを施す方法が、特開平第1-287021号では、粉末またはペレット状の融点40～90℃のワックス類を流動層コーティング装置を用いてワックスの融点以上に加熱し被覆する方法が、特開平第2-142735号では、機械的攪拌により融点40℃以上の脂質粉末状をコーティングする方法が提案されているが、これらは徐放性製剤または苦味のマスキングを目的とした製剤で、腸溶性コーティング剤との組み合わせについては触れられていない。

【0008】また、特開平第2-292229号では、難溶性薬物と常温で固体の高級脂肪酸と腸溶性コーティング剤と界面活性剤の混合物を加熱し、高級脂肪酸の溶融下に練合して顆粒剤を製することで持続性製剤が得られることが開示されているが、耐酸性のある腸溶性製剤に関するものではない。特開昭第62-181214号においても、融点30～100℃の低融点物質として油脂類、脂肪酸類、高級アルコール類があげられ、これらの粉粒状の低融点物質を核としてそのまわりに薬物を溶融により付着造粒させ、さらに攪拌転動下に得られた粒子を加熱しタルク等を散布し被覆することで、徐放性粒状物を製する方法が開示されており、この方法では、タルクでの被覆に際して、10 $\mu$ m以下に微粉碎した腸溶性コーティング剤を併用することで、被膜の緻密化としているが、耐酸性のある腸溶性製剤に関するものではない。

【0009】本発明者らは、上記の点に鑑みて鋭意研究した結果、液体状の可塑剤を散布しつつ微粉末状の腸溶性コーティング剤により被覆することで、短時間で乾燥を必要としない無溶媒コーティングにより耐酸性を有する腸溶性製剤が得られることを見出し、本発明を完成するに至った。

【0010】

【課題を解決するための手段】すなわち、本発明は、固形薬剤に、液体状の可塑性剤を散布しつつ微粉末状の腸溶性コーティング剤を被覆した腸溶性製剤を提供するものである。

【0011】また、本発明は、前記固形薬剤が、顆粒剤、細粒剤または薬物原体である腸溶性製剤を提供するものである。

【0012】さらに、本発明は、前記液体状の可塑性剤が、クエン酸トリエチルである腸溶性製剤を提供するものである。

【0013】また、本発明は、前記微粉末状の腸溶性コーティング剤の粒子径が、 $10\mu\text{m}$ 以下である腸溶性製剤を提供するものである。

【0014】以下、本発明を詳述する。本発明による腸溶性製剤は、固形薬剤に、常温で液体状の可塑性剤を散布しながら、微粉末状の腸溶性コーティング剤により被覆することを特徴とするものである。

【0015】本発明に用いる可塑性剤としては、疎水性で微粉末状の腸溶性コーティング剤を融着させる性質を有するものであれば特に限定されるものではない。例えば、クエン酸トリエチル、トリアセチン、ジブチルフタレートなどが挙げられる。これらの中では、腸溶性コーティング剤を融着させる効果の大きいクエン酸トリエチルが好ましい。これらの可塑性剤は、1種または2種以上の混合物として使用することができる。

【0016】また、腸溶性コーティング剤の被覆に際して、高級アルコール類、高級脂肪酸類、グリセリン脂肪酸エステル類などの疎水性のワックス類を添加することで、得られる腸溶性製剤の耐水性を向上させることができる。

【0017】さらに、ポリエチレングリコールなどの水溶性の多価アルコール類を併用することで徐放性製剤とすることもできる。

【0018】本発明は、微粉末上の腸溶性コーティング剤を散布して被覆するため、適用できる好ましい固形薬剤は、顆粒剤、細粒剤または薬物原体などであり、これらは球形に近いものほど耐酸性を得るのに必要とする腸溶性コーティング剤の量が少なくてよいので好ましい。

【0019】本発明に用いる腸溶性コーティング剤は、好ましくは $10\mu\text{m}$ 以下の微粉末であればよく、例えば、セルロース系ではセルロースアセテートフタレート(CAP)、セルロースアセテートトリメリテート(CAT)、ヒドロキシプロピルメチルセルロースフタレート(HPMCP)、ヒドロキシプロピルメチルセルロースアセテートサクシネート(HPMCAS)、カルボキシメチルエチルセルロース(CMEC)が、ビニル系ではポリビニルアルコールアセテートフタレート(PVAP)が、アクリル系ではメタアクリル酸とアクリル酸エチルの共重合体が使用できる。平均粒径が $10\mu\text{m}$ を越

えるとコーティング剤が顆粒にうまく付着せずコーティングできない場合がある。

【0020】これらのコーティング剤の内では、軟化温度が低く造膜性に優れるヒドロキシプロピルメチルセルロースアセテートサクシネート(HPMCAS)が適している。

【0021】また、腸溶性コーティング剤以外的高分子の微粉末、例えば、エチルセルロース、アクリル系ポリマーを併用することで徐放性製剤とすることもできる。

【0022】本発明を実施するには、溶媒を用いないため多大な乾燥能力を必要とせず、散布した微粉末状の腸溶性コーティング剤の展延と融着のために、ある程度の加熱と攪拌能力を有することが好ましく、例えば、遠心流動コーティング装置、パンコーティング装置、流動層コーティング装置などが挙げられる。これらのコーティング装置の中では、適度な攪拌能力を有する遠心流動コーティング装置が適している。

【0023】腸溶性コーティング剤による被覆は、例えば、顆粒あるいは細粒状の固形薬剤を、前述したような遠心流動コーティング装置で攪拌転動させながら、常温で液体または加熱溶解した液体状の可塑性剤を散布またはスプレーし、同時に $10\mu\text{m}$ 以下の腸溶性コーティング剤を散布し固形薬剤を被覆する。これらの一連の操作は、数回に分けてそれぞれ組成を変化させて実施することもできる。また、被覆時の顆粒同士の粘着を防止する目的で、タルク、アエロジル( $\text{SiO}_2$ )、ステアリン酸マグネシウム、コーンスターチなどの散布を併用してもよい。

【0024】本発明における可塑性剤と腸溶性コーティング剤の重量比率、および、固形薬剤に対するコーティング量は、耐酸性を得る上で重要な因子であるが、適用する薬物の水溶性、固形薬剤(顆粒剤等)中の薬物の組成比などにより大きく変化するが、概ね、可塑性剤：腸溶性コーティング剤=2：8～8：2の範囲にあり、これ以上可塑性剤の組成比が高まると、日本薬局方第2液(pH 6.8)での崩壊性が失われ、これ以下では腸溶性コーティング剤の融着が不十分となる。

【0025】コーティング量は固形薬剤に対する被覆した腸溶性コーティング剤の重量比で、概ね、10～50重量%の範囲にある。

【0026】なお、本発明では、腸溶性コーティング剤を散布してコーティングするため、コーティング量が増加してもその処理時間は著しく短い。

【0027】以上のようにして得られた本発明の腸溶性製剤は、この後さらに他の高分子化合物により被覆してもよい。また、これらのコーティングに通常製剤学的に認められる薬物、添加剤(可塑性剤、着色剤、顔料、粘着防止剤(タルク)、油脂類等)を加えてもよい。

【0028】

【実施例】次に実施例により本発明を更に具体的に説明

するが本発明はこれらの実施例に限定されるものではない。なお、実施例中の部数及び%は重量%である。

【0029】〔実験1：VB<sub>2</sub>含有顆粒の作製〕核顆粒(NP-W101 20-24# フロイント産業(株)社製)200gを遠心流動コーティング装置(CFcoater CF-360 フロイント産業(株)社製)に仕込み、ヒドロキシプロピルセルロース5%水溶液を噴霧しながら、VB<sub>2</sub>75g、コーンスターチ1175gを均一に混合した粉体を散布して顆粒を作製した。この顆粒中のVB<sub>2</sub>の含有量は2%であった。

【0030】〔実施例1〕実験1で作製したVB<sub>2</sub>2%含有顆粒400gを遠心流動コーティング装置(CFcoater CF-360 フロイント産業(株)社製)に仕込み、吸気温度60℃、品温40℃、回転数200rpmで、クエン酸トリエチル60gを10g/minの速度でスプレーしながら、ヒドロキシプロピルメチルセルロースアセテートサクシネート(平均粒径5μm：AS-MF 信越化学工業(株)製)120g、タルク240gを均一に混合した粉体を60g/minの速度で添加してコーティングを行った。収率は95%であった。処理時間は6minであった。このコーティング顆粒を日本薬局方12溶出試験法に従い第1液での2時間後の溶出率を測定した結果、その溶出率は1.5%であり優れた耐酸性を示した。また、日本薬局方12崩壊試験法に従い、その顆粒の第2液での崩壊時間を測定したところ10minであり、腸溶性を示すことが判った。

【0031】〔実施例2〕実験1で作製したVB<sub>2</sub>2%含有顆粒400gを遠心流動コーティング装置(CFcoater CF-360 フロイント産業(株)社製)に仕込み、吸気温度60℃、品温40℃、回転数200rpmで、トリアセチン120gを20g/minの速度でスプレーしながら、ヒドロキシプロピルメチルセルロースアセテートサクシネート(平均粒径5μm：AS-MF 信越化学工業(株)製)120g、タルク240gを均一に混合した粉体を60g/minの速度で添加してコーティングを行った。収率は95%であった。処理時間は6minであった。このコーティング顆粒を日本薬局方12溶\*

〔コーティング液組成〕

ヒドロキシプロピルメチルセルロースアセテートサクシネート(AS-MF 信越化学工業(株)製)	7.00 %
クエン酸トリエチル	1.96
タルク	2.10
ラウリル硫酸ナトリウム	0.21
水	88.73
合計	100.00

【0034】

【発明の効果】従来の腸溶コーティングは、腸溶性コーティング剤の有機溶剤溶液または水性ラテックスあるいは水分散液により行われている。このため、スプレーに長時間を要し、また、溶媒の乾燥時間も必要で、薬物に※50

\* 出試験法に従い第1液での2時間後の溶出率を測定した結果、その溶出率は1.5%であり優れた耐酸性を示した。また、日本薬局方12崩壊試験法に従い、その顆粒の第2液での崩壊時間を測定したところ10minであり、腸溶性を示すことが判った。

【0032】〔実施例3〕実験1で作製したVB<sub>2</sub>2%含有顆粒400gを遠心流動コーティング装置(CFcoater CF-360 フロイント産業(株)社製)に仕込み、吸気温度60℃、品温40℃、回転数200rpmで、クエン酸トリエチルのエタノール50%溶液120gを20g/minの速度でスプレーしながら、ヒドロキシプロピルメチルセルロースアセテートサクシネート(平均粒径5μm：AS-MF 信越化学工業(株)製)120g、タルク120gを均一に混合した粉体を40g/minの速度で添加してコーティングを行った。収率は98%であった。処理時間は6minであった。このコーティング顆粒を日本薬局方12溶出試験法に従い第1液での2時間後の溶出率を測定した結果、その溶出率は1.0%であり優れた耐酸性を示した。また、日本薬局方12崩壊試験法に従い、その顆粒の第2液での崩壊時間を測定したところ11minであり、腸溶性を示すことが判った。

【0033】〔比較例1〕実験1で作製したVB<sub>2</sub>顆粒へヒドロキシプロピルメチルセルロースアセテートサクシネート(AS-MF 信越化学工業(株)製)に下記組成のコーティング液を用いて水分散系コーティングを実施した。VB<sub>2</sub>顆粒400gを流動層コーティング装置(Multiplex MP-01 (株)パウレック社製)に仕込み、吸気温度80℃、排気温度35℃、コーティング液スプレー速度25g/minでヒドロキシプロピルメチルセルロースアセテートサクシネート(AS-MF 信越化学工業(株)製)の素顆粒に対するコーティング量(30%)が実施例1と同一になるまでコーティングを実施した。コーティング収率は92%であり、コーティング時間68min要した。その後、後乾燥として60℃、30min乾燥を実施した。コーティング顆粒作製に要した合計時間は98minであった。

※よって、水あるいは有機溶剤との接触を嫌うか、乾燥時の加熱を嫌うなどの問題点を有していた。

【0035】本発明によれば、短時間で乾燥を必要としない無溶媒コーティングにより耐酸性を有する腸溶性製剤が得られる。したがって、溶媒の乾燥が不要(乾燥時

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加熱無し)でコーティング時間が短いため製造工程の短縮化を図ることができる。また、無溶媒コーティングにより水および有機溶剤に対して不安定な薬物に適用でき

る。さらに、水系腸溶性コーティングで分散剤として汎用されている界面活性剤なども使用する必要がないという利点を有する。

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